

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



(7)

AI

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : B01D 15/08	A1	(11) International Publication Number: WO 92/16276 (43) International Publication Date: 1 October 1992 (01.10.92)
(21) International Application Number: PCT/US92/01864 (22) International Filing Date: 9 March 1992 (09.03.92) (30) Priority data: 668,831 13 March 1991 (13.03.91) US (60) Parent Application or Grant (63) Related by Continuation US 668,831 (CIP) Filed on 13 March 1991 (13.03.91) (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 E. Lincoln Avenue, Rahway, NJ 07065 (US).	(72) Inventors; and (75) Inventors/Applicants (for US only) : HAYTKO, Peter, N. [US/US]; 1811 Main Street, Rahway, NJ 07065 (US). WILDMAN, Arthur, S., Jr. [US/US]; 33 Hillcrest Road, Martinsville, NJ 08836 (US). (74) Agent: WINOKUR, Melvin; 126 E. Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>	
(54) Title: PROCESS FOR PURIFICATION OF HMG-CoA REDUCTASE INHIBITORS (57) Abstract A process for the purification of an HMG-CoA reductase inhibitor employing preparative high performance liquid chromatography as well as a pharmaceutical composition comprising the HMG-CoA reductase inhibitor and pharmaceutically acceptable carrier.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	MI	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark	MG	Madagascar		
ES	Spain				

5

-1-

10

TITLE OF THE INVENTION

PROCESS FOR PURIFICATION OF HMG-CoA REDUCTASE
INHIBITORS

15 BACKGROUND OF THE INVENTION

This is a continuation in part of U. S.
Serial Number 07/668,831, filed March 13, 1991.

High product purity is an important criterion
for the manufacture of a safe and effective pharma-
20 ceutical. HMG-CoA reductase inhibitors, such as
lovastatin, simvastatin and pravastatin, are a
recently introduced new class of cholesterol-lowering
agents that effectively lower plasma cholesterol but
must be taken on a long term basis. Thus it is
25 particularly critical that HMG-CoA reductase
inhibitors be administered in the highest possible
purity.

30

- 2 -

Standard methods for the purification of organic molecules involve multiple recrystallization steps and employ large amounts of organic solvents. It would be highly desirable to employ a purification process that would yield a product purity of at least 99.5%, use no more than one crystallization with a recyclable solvent and be adaptable to high production volume.

High performance liquid chromatography (HPLC) is commonly used for the analytical determinations of compound purity. HPLC for large scale industrial solution preparations (preparative HPLC) has been employed in the separation and purification of proteins but it is believed not to have been employed in the large scale purification of relatively small molecules such as HMG-CoA reductase inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a process for the purification of HMG-CoA reductase inhibitors by high performance liquid chromatography to yield a product of purity of at least 99.5%. The HMG-CoA reductase inhibitors within this invention include, but are not limited to, lovastatin, simvastatin, pravastatin, fluvastatin and mevastatin. The HPLC process of this invention offers a significant advantage in that no recrystallization is required to obtain a purity of at least 99.5% and typically only crystallization is employed. In addition, the HPLC process of this invention may be carried out with only one organic solvent, thus minimizing the need for recycling of solvent.

- 3 -

The process of this invention herein may employ either normal phase HPLC or reverse phase HPLC. For HMG-CoA reductase inhibitors exhibiting a tetrahydro-pyranone ring, such as lovastatin and simvastatin, the reverse phase procedure is preferred. The column packing may be uncoated silica, coated silica or porous graphitic carbon. The term coating as used herein includes both a physical and a chemical bonding of the binding group.

The crude HMG-CoA reductase inhibitor of approximately 85% or higher purity is dissolved in an organic solvent or a solution of an organic solvent and water. The mixture may be buffered to a pH between 2 and 9 with an organic or inorganic salt. Buffers may include, but are not limited to, Tris-acetate, or acetic acid/ammonia. The resulting solution is placed on an HPLC column. The column packing may be regular or irregular in shape. The diameter of the packing material may range from about 1 μm to about 100 μm . Preferably, the packing material is irregularly-shaped octadecylsilane and the diameter of the packing material is between about 3 μm and about 30 μm .

The column packings include, but are not limited to, silica, octylsilane, dimethylsilane, octadecylsilane, cyano-silane, or polystyrene-divinylbenzene copolymer with an organosilyl stationary phase.

30

- 4 -

The column diameter may vary from 5 cm to 80 cm. The usual column length is approximately 25 cm. The column length may be extended as needed to effect the separation. Lengthening of the column may be accomplished by linking additional columns in series.

In general, the column is packed with the coated or uncoated silica in the following manner: the packing material is slurried in ethanol. The slurry is then transferred into the column and compressed at 55 bar using Dynamic Axial Compression (D.A.C.*), a procedure described in U. S. Patent 3,996,609 and French Patent 73.07278. Alternatively, the column may be radially compressed. The ethanol is displaced with mobile phase. After packing the column is tested by collecting serial fractions and evaluating those fractions by standard analytical techniques.

The eluant is an organic solvent or a solution of an organic solvent and water which may also include a buffer of pH 2 to pH 9. The eluant is generally the same solvent or solvent mixture as the dissolving solvent but, if desired, the eluant may have a different composition. Preferably the eluant contains the same organic solvent and aqueous modifiers as the dissolving solvent. If desired, a gradient elution of the mobile phase may be employed to more rapidly elute the HMG-CoA reductase inhibitor through the column. The chromatography may be carried out at an operating temperature appropriate to the solvents employed, however a range of about 15° to about 60°C is preferred. In the preferred embodiment, isothermal conditions are maintained throughout the separation. Detection of the HMG-CoA

- 5 -

reductase inhibitor may be by spectroscopic means or by other physical means such as optical rotation or refractive index. The preferred means are by ultraviolet absorption or refractive index. After the HMG-CoA reductase inhibitor peak of interest is collected, a portion of the solvent is removed and an aqueous solution is added to crystallize the HMG-CoA reductase inhibitor. Generally, about one-third of the solvent mixture is removed and water is employed to crystallize the HMG-CoA reductase inhibitor. Alternatively about two-thirds of the solvent mixture is removed to crystallize the HMG-CoA reductase inhibitor. The crystallized inhibitor is then filtered and dried to yield a product of purity of at least 99.5% and with an overall yield of about 90%. Product purity is determined by HPLC relative to a reference standard. Yield is determined by weight.

The crude HMG-CoA reductase inhibitor is prepared following any of the literature procedures well known to those skilled in this art. Packing materials of uncoated or coated silica are commercially available. Porous graphitic carbon as a packing material is also commercially available in pre-packed columns.

The organic solvent, employed as the dissolving solvent or the eluant, is selected from acetonitrile, methanol, ethanol, acetone, tetrahydrofuran, isopropanol, ethyl acetate, methylene chloride, chloroform or a mixture thereof. The percent of organic solvent in an organic solvent/water mixture may vary from about 10% to about 90% organic solvent, preferably 65% to 75% organic solvent.

- 6 -

The present invention is also directed to purified forms of HMG-CoA reductase inhibitors or their salts which have a purity of at least 99.5%. In one class of the invention are lovastatin, simvastatin and pravastatin of purity 99.5% or better. Also included with the present invention are pharmaceutical compositions containing a HMG-CoA reductase inhibitor or a salt thereof of purity of at least 99.5% and particularly lovastatin, simvastatin and pravastatin of purity of at least 99.5%.

If desired the amount of any residual solvent, particularly acetonitrile, may be decreased by dissolution of the purified HMG-CoA reductase inhibitor in aqueous methanol and crystallizing therefrom as shown below in Example 6.

The pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide.

The purified compounds of this invention may also be administered in combination with other cholesterol lowering agents such as those which inhibit an enzymatic pathway in the biosynthesis of cholesterol. Example of such agents would include

- 7 -

but are not limited to squalene synthetase inhibitors, HMG-CoA synthase inhibitors, and squalene epoxidase inhibitors. Illustrative of such inhibitors are the squalene synthetase inhibitors described in U. S. Patents 5,053,425; 5,055,487 and 5,026,554. Other cholesterol lowering agents that may be administered include niacin, probucol, and the fibric acids, clofibrate and gemfibrozil. Appropriate daily dosages for adults are niacin (2-8 gm), probucol (up to 1000 mg), clofibrate (up to 2 gm) and gemfibrozil (800-1500 mg).

The compounds of this invention may also be coadministered with pharmaceutically acceptable nontoxic cationic polymers capable of binding bile acids in a non-reabsorbable form in the gastrointestinal tract. Examples of such polymers include cholestyramine, colestipol and polymethyl-(3-trimethylaminopropyl)imino-trimethylene dihalide. The relative amounts of the compounds of this invention and these polymers is between 1:100 and 1:15,000.

EXAMPLE 1

4.6 g of crude lovastatin was dissolved in 200 mL of 70:30 acetonitrile/water which was injected onto a 5 cm diameter, 25 cm long stainless steel column packed with 10 μ m, irregular-shaped octadecylsilane HPLC packing material (RG1010-C18, The PQ Corporation, Conshohocken, PA). The eluant was 70:30 acetonitrile/water and the flow rate was approximately 150 mL/min. The lovastatin fraction was collected in a volume of 260 mL using UV

- 8 -

detection at 254 nm. The lovastatin fraction was eluted at $K' = 2.0-3.0$. K' , the capacity factor, is related to the retention time as described in USP - XXII (p. 1565; 1990). The resulting solution was concentrated by removal of one-third of the solvent, and the lovastatin was crystallized by the addition of water to give an acetonitrile concentration of approximately 25-30%. The pure lovastatin product was recovered by filtration and drying. Lovastatin with a purity of 99.7% w/w was recovered in an overall yield of 90%.

EXAMPLE 2

Lovastatin at a concentration of 2.3 g/100 mL was dissolved in a mixture of 70% acetonitrile/30% 0.02 M Tris-acetate (pH 7.4). The solution was loaded onto a 5 cm diameter, 25 cm long stainless steel column packed with 10 μ m, irregular-shaped octadecylsilane (RG1010-C18, The PQ Corporation, Conshohocken, PA). The eluant was 70% acetonitrile/30% water and the flow rate was approximately 150 mL/minute. Detection was by ultraviolet absorption at 254 nm. Lovastatin was eluted at $K' = 2.0-3.0$. The lovastatin peak was collected and one third the volume was removed by vacuum distillation at $\leq 40^\circ\text{C}$. Water was added to bring the acetonitrile concentration to 25-30%. The lovastatin was filtered and dried in vacuo at $\leq 40^\circ\text{C}$. Lovastatin with a purity of $\geq 99.7\%$ was recovered in an overall yield of $\geq 90\%$.

- 9 -

EXAMPLE 3

4.6 g of crude lovastatin was dissolved in 200 mL of 70:30 acetonitrile/water buffered with 0.02 M Tris-acetate (pH 7.5). The solution was loaded onto a 5 cm diameter, 25 cm long column packed with 10 μ m, irregular-shaped octadecylsilane HPLC packing (RG1010-C18, The PQ Corporation, Conshohocken, PA). The eluant was 70:30 acetonitrile/water and the flow rate was approximately 150 mL/min. The lovastatin fraction was collected in a volume of 265 mL using UV detection at 254 nm. The lovastatin peak eluted at $K' = 2.0-3.0$. The resulting solution was concentrated by removal of one third of the solvent. Lovastatin was crystallized by the addition of water to give an acetonitrile concentration of approximately 25-30%. The pure lovastatin product was recovered by filtration and drying. Lovastatin with a purity of 99.7% w/w was recovered in an overall yield of 91%.

EXAMPLE 4

4.6 g of crude lovastatin was dissolved in 200 mL of 70:30 acetonitrile/water buffered with 0.02 M Tris-acetate (pH 7.5). The solution was loaded onto a 5 cm diameter, 25 cm long column packed with 10 μ m, irregular-shaped octadecylsilane HPLC packing (RG1010-C18, The PQ Corporation, Conshohocken, PA). The eluant was 70:30 acetonitrile/water and the flow rate was approximately 150 mL/min. The lovastatin fraction was collected in a volume of 265 mL using UV detection at 254 nm. The lovastatin peak eluted at $K' = 2.0-3.0$. The resulting solution was concentrated

- 10 -

by removal of two-thirds of the solvent, which crystallized the lovastatin. The pure lovastatin product was recovered by filtration and drying. Lovastatin with a purity of 99.7% w/w was recovered
5 in an overall yield of 91%.

EXAMPLE 5

Lovastatin at a concentration of 4.5 g/100 mL was dissolved in a mixture of 70% acetonitrile/30%
10 0.02 M Tris-acetate (pH 7.2). The 40°C solution was injected onto a 5 cm diameter, 25 cm long stainless steel column packed with 10-20 µm, irregular-shaped octadecylsilane HPLC packing (RG1020-C18, The PQ
15 Corporation, Conshohocken, PA). The eluant was 70:30 acetonitrile/water and the flow rate was approximately 150 mL/min. The media and column were isothermally maintained at 40°C. The lovastatin fraction was collected in a volume of 500 mL using UV
20 detection at 254 nm. The lovastatin fraction eluted at $K' = 2.0-3.0$. The resulting solution was concentrated by removal of two-thirds of the solvent and the lovastatin crystallized. The lovastatin was recovered by filtration and drying. Lovastatin with
25 a purity 99.8% w/w was recovered in an overall yield of 90%.

- 11 -

EXAMPLE 6

6.0 g of the purified lovastatin prepared as described in Example 5 was dissolved in 100 mL of 95% methanol/5% water at 60° C. The 60° C solution was crystallized by the addition of an equal volume of 65% water/35% methanol. The resulting crystalline mixture was concentrated to one half volume. Lovastatin was recovered by filtration and drying. 5.98 g of lovastatin was recovered.

EXAMPLE 7

Simvastatin may be purified to a crystalline form of purity greater than 99.5% using procedures analogous to those described in Example 5. Crude simvastatin is used in place of crude lovastatin.

EXAMPLE 8

Pravastatin may be purified to a crystalline form of purity greater than 99.5% using a procedure analogous to that in Example 5, but substituting crude pravastatin for the crude lovastatin.

- 12 -

WHAT IS CLAIMED IS:

1. A process for purifying a crude HMG-CoA reductase inhibitor which comprises:

- 5 (1) placing a solution of the crude HMG-CoA reductase inhibitor on a high performance liquid chromatography column wherein said column is packed with silica optionally coated with a stationary phase selected from a group consisting of a triorganosilyl, a
10 cyanoorganosilyl or a polystyrene-divinylbenzene copolymer with an organosilyl, or said column is packed with a porous graphitic carbon;
- 15 (2) eluting with a solvent mixture comprising:
 (a) an organic solvent selected from a group consisting of acetonitrile, methanol, ethanol, acetone, tetrahydrofuran, isopropanol, ethyl acetate, methylene chloride or chloroform,
20 or a mixture thereof and optionally
 (b) water or an aqueous solution selected from: phosphoric acid, acetic acid;
- 25 (3) removing about 30 to 35 percent of the solvent mixture from the eluted fraction containing HMG-CoA reductase; and
- 30 (4) treating the eluted fraction containing HMG-CoA reductase inhibitor fraction with water to crystallize the HMG-CoA reductase inhibitor.

- 13 -

2. A process of Claim 1 wherein the HMG-CoA reductase inhibitor is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin or mevastatin.

5

3. A process of Claim 2 wherein the HMG-CoA reductase inhibitor is selected from lovastatin or simvastatin.

10

4. A process of Claim 2 wherein the HMG-CoA reductase inhibitor is lovastatin.

15

5. A process of Claim 3 wherein the column is packed with a silica coated with an octadecylsilane stationary phase.

6. A process of Claim 5 wherein the solvent mixture is acetonitrile and water.

20

7. A process of Claim 6 wherein the solvent mixture is 70% acetonitrile and 30% water.

25

8. A process of Claim 7 wherein the operating temperature of the chromatography is between 15° to 60°C.

30

9. A process of Claim 8 wherein about one-third of the solvent mixture is removed from the eluted fraction containing the HMG-CoA reductase inhibitor.

- 14 -

10. A process of Claim 1 further comprising the filtering and drying of the HMG-CoA reductase inhibitor to yield a product of purity \geq 99.5%.

5 11. A process for purifying a crude HMG-CoA reductase inhibitor which comprises:

(1) placing a solution of the crude HMG-CoA reductase inhibitor on a high performance liquid chromatography column wherein said
10 column is packed with silica optionally coated with a stationary phase selected from a group consisting of a triorganosilyl, a cyanoorganosilyl or a polystyrene-polystyrene-divinylbenzene copolymer with an
15 organosilyl, or said column is packed with a porous graphitic carbon;

(2) eluting with a solvent mixture comprising:
(a) an organic solvent selected from a
20 group consisting of acetonitrile, methanol, ethanol, acetone, tetrahydrofuran, isopropanol, ethyl acetate, methylene chloride or chloroform, or a mixture thereof and optionally

(b) water or an aqueous solution selected from: phosphoric acid, acetic acid; and

25 (3) removing about 60 to 65% of the solvent mixture from the eluted fraction containing HMG-CoA reductase inhibitor to crystallize the HMG-CoA reductase inhibitor.

30 12. An HMG-CoA reductase inhibitor of purity at least 99.5% or a pharmaceutically acceptable salt thereof.

- 15 -

13. A compound of Claim 12 wherein the HMG-CoA reductase inhibitor is selected from the group consisting of lovastatin, simvastatin and pravastatin or a pharmaceutically acceptable salt thereof.

14. A compound of Claim 13 wherein the HMG-CoA reductase inhibitor is lovastatin.

15. A compound of Claim 13 wherein the HMG-CoA reductase inhibitor is simvastatin.

16. A compound of Claim 13 wherein the HMG-CoA reductase inhibitor is pravastatin.

17. An HMG-CoA reductase inhibitor purified by a process comprising high performance liquid chromatography and wherein the HMG-CoA reductase inhibitor has a purity of at least 99.5%.

18. A pharmaceutical composition comprising a nontoxic therapeutically effective amount of a compound of Claim 12 and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition comprising a nontoxic therapeutically effective amount of a compound of Claim 12 in combination with a pharmaceutically acceptable nontoxic cationic polymer capable of binding bile acids in a non-reabsorbable form in the gastrointestinal tract and pharmaceutically acceptable carrier.

- 16 -

20. A pharmaceutical composition comprising
a nontoxic therapeutically effective amount of a
compound of Claim 12 in combination with a nontoxic
therapeutically effective amount of a cholesterol
lowering agent selected from the group consisting of:

- (a) Squalene synthetase inhibitor;
- (b) HMG-CoA synthetase inhibitor;
- (c) Squalene epoxidase inhibitor;
- (d) Probucol;
- (e) Niacin;
- (f) Gemfibrozil; and
- (g) Clofibrate.

INTERNATIONAL SEARCH REPORT

International Association PCT/US92/01364

I. CLASSIFICATION OF SUBJECT MATTER (In several classification systems apply, indicate all) According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5): B01D 15/08 US Cl.: 210/656; 435/125					
II. FIELDS SEARCHED <div style="text-align: center; font-size: small;">Minimum Documentation Searched</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 20%; border: none;">Classification System:</td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; vertical-align: top;">U.S.</td> <td style="border: none; vertical-align: top;">210/198.2, 635, 656; 422/70; 435/125; 436/161; 514/356, 451; 514/460, 543, 571, 642, 643, 712, 824; 549/292</td> </tr> </table> <div style="text-align: center; font-size: x-small;">Documentation Searched other than Minimum Documentation to the extent that such documents are included in the fields searched</div>		Classification System:	Classification Symbols	U.S.	210/198.2, 635, 656; 422/70; 435/125; 436/161; 514/356, 451; 514/460, 543, 571, 642, 643, 712, 824; 549/292
Classification System:	Classification Symbols				
U.S.	210/198.2, 635, 656; 422/70; 435/125; 436/161; 514/356, 451; 514/460, 543, 571, 642, 643, 712, 824; 549/292				

(III) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No. 1
Y	US, A, 4,533,494 (UCHIYAMA) 06 August 1985 See the entire document	1-11
X Y	US, A, 4,997,755 (WILLIAMSON) 05 March 1991 See the entire document	2-8, 12-14, 17 1, 9-11, 15-16
Y	US, A, 4,833,258 (SMITH) 23 May 1989 See the entire document	1-11
Y	US, A, 4,965,200 (CHEN) 23 October 1990 See the entire document	1-11
Y	US, A, 4,719,229 (REAMER) 12 January 1988 See the entire document	1-11
X	US, A, 4,231,938 (MONAGAN) 04 November 1980 See the entire document	12-14
X, P	US, A, 5,089,523 (VARMA) 18 February 1992 See the entire document	1, 18-20
X, E	US, A, 5,099,035 (SAUNDERS) 24 March 1992 See the entire document	12, 18-20

- * Special categories of cited documents:**

 - "A" document defining the general state of the art which is not considered to be of particular relevance
 - "E" earlier document but published on or after the international filing date
 - "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 - "O" document referring to an oral disclosure, use, exhibition or other means
 - "P" document published prior to the international filing date but later than the priority date claimed

† Prior document published after the international filing date or priority date and not in conflict with the invention but cited to understand the principles or theory underlying the invention

 - "1" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
 - "2" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 - "3" document member of the same patent family

IV. CERTIFICATION	
Date of the Actual Completion of the International Search 28 April 1992 International Searching Authority ISA/US	Date of Mailing of the International Search Report <div style="font-size: large; font-weight: bold; text-align: center;">15 JUN 1992</div> Signature of Authorized Officer <i>Nguyen Huu</i> <div style="text-align: center;">NGUYEN HUU</div> for Sun Uk Kim INTERNATIONAL DIVISION

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X, E	US, A, 5,102,911 (LEE) 07 April 1992 See the entire document	12,16-20
X	The Merck Index, 11th Edition, Published 1989 (Rahway, New Jersey) See compounds 5460, 7712, 8491	12-16

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____ because they relate to subject matter not required to be searched by the Authority, namely:

2. ☐ Claim numbers _____ because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out. Specifically:

3. ☐ Claim numbers _____ because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Searching Authority found multiple inventions in the international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid. Specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim number(s):

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remarks on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.